HIV-AIDS
An Over View

BY

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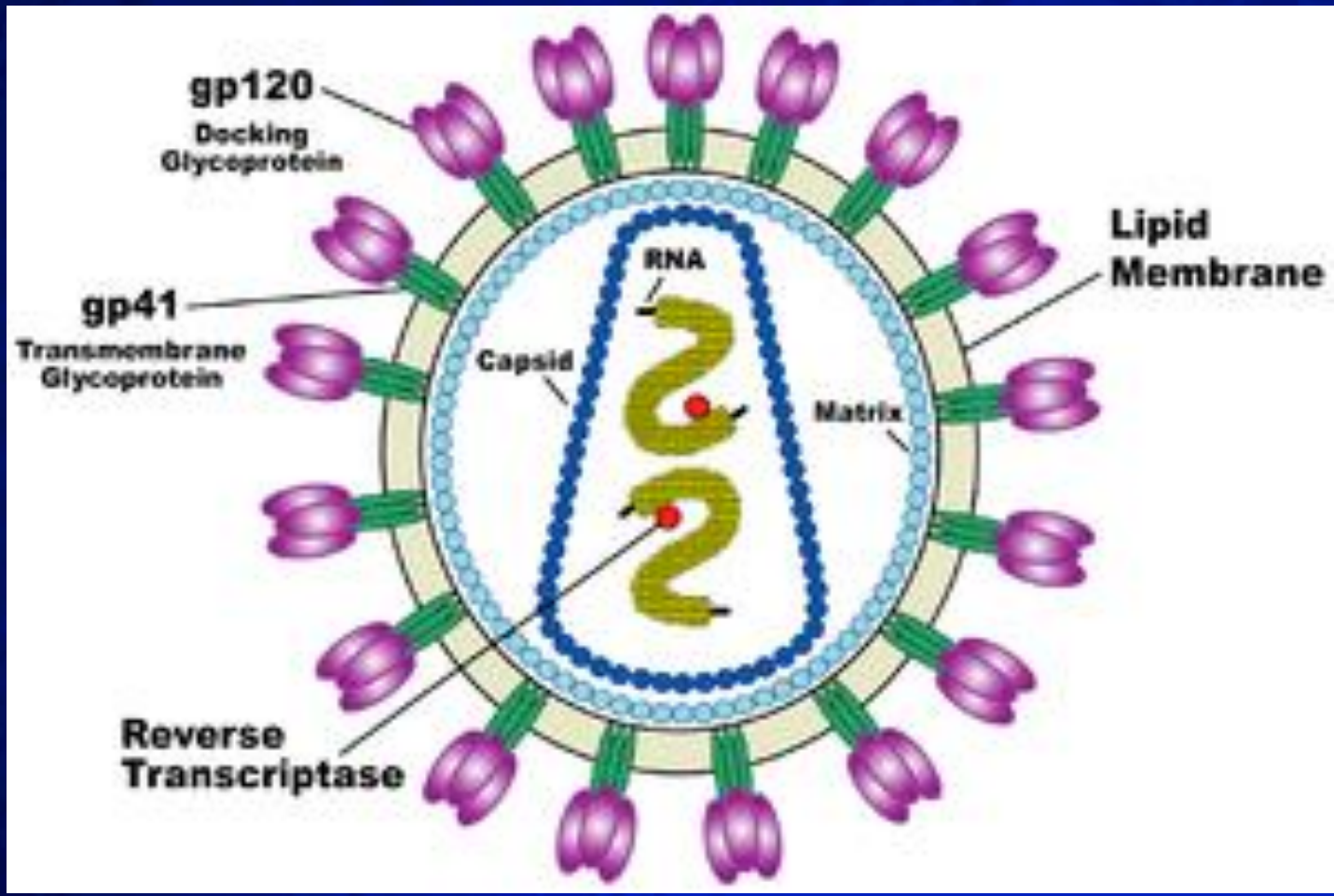
HIV

- It is a retrovirus contains two copies of RNA.

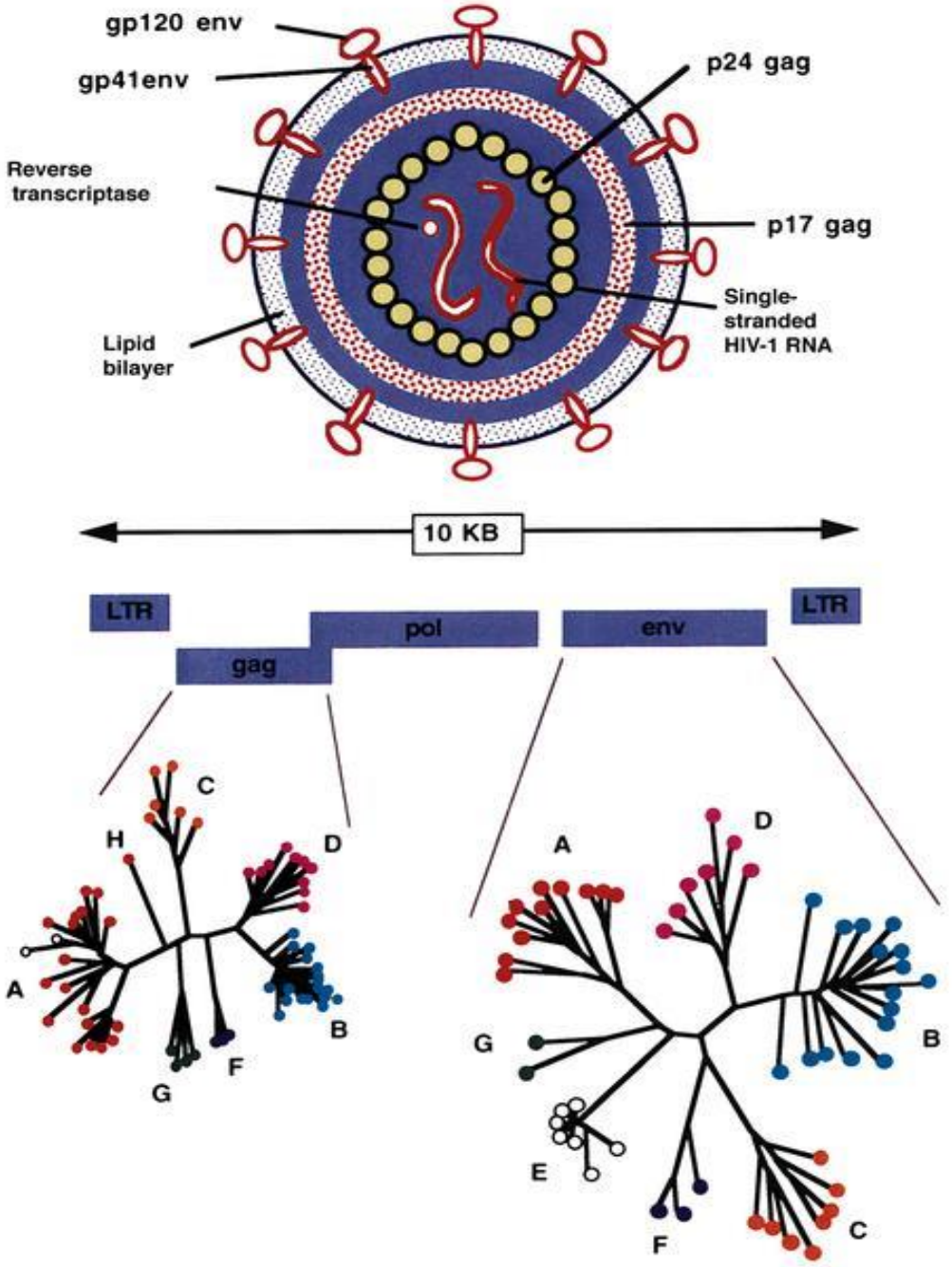


HIV

has 2 main variants

HIV-1

HIV-2



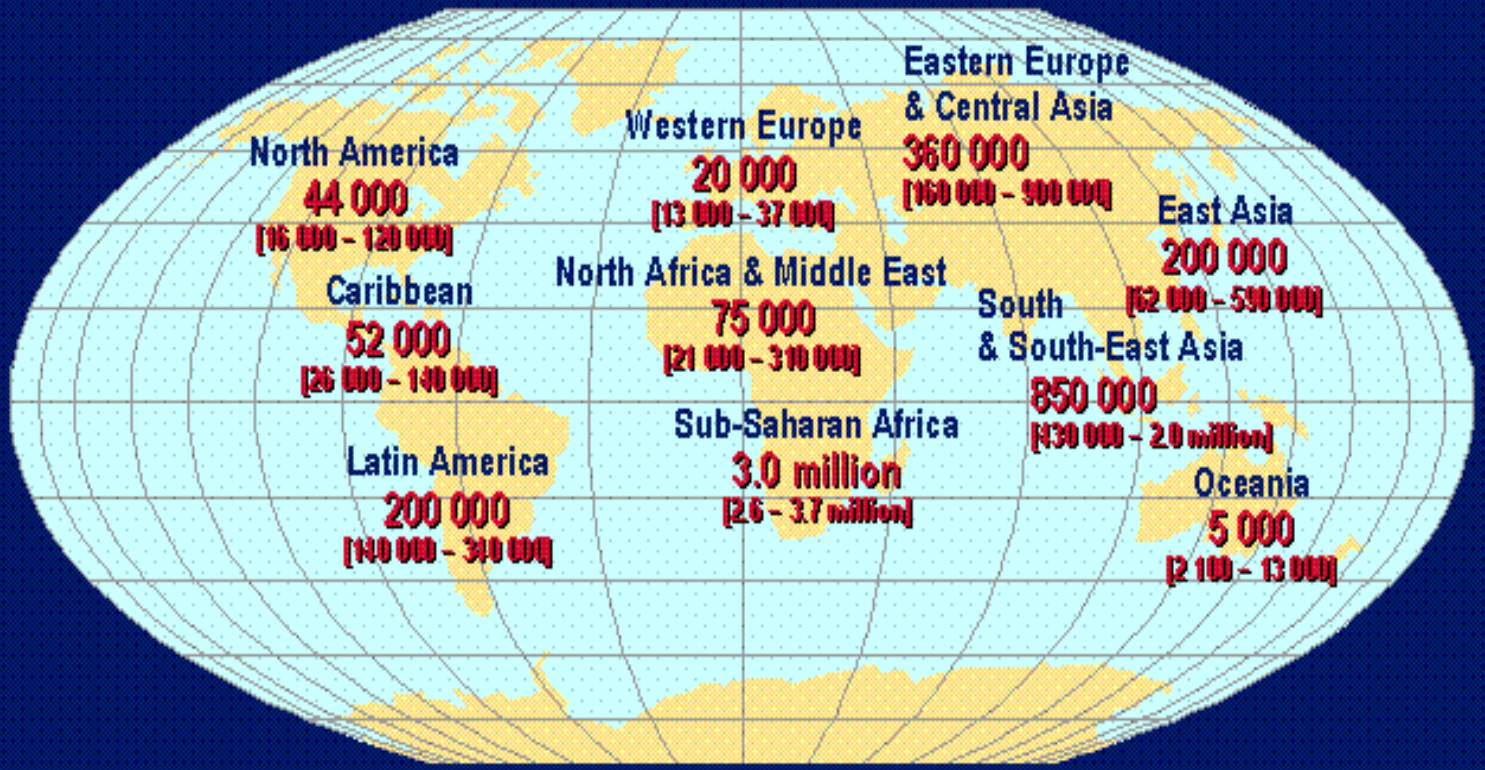
HIV-1

-Predominates in most parts of the world.
-Highly infectious.
-Has different subtypes according to virulence.

HIV-2

-Endemic in West Africa.
- Less infectious and less pathogenic than HIV-1
- Has cross reactivity and protective role against HIV-1.

Estimated number of adults and children newly infected with HIV during 2003



Total: 4.8 (4.2 – 6.3) million

UNAIDS

UNAIDS/04.03E-E-5 - July 2004

World Health Organization

Adults and children estimated to be living with HIV as of end 2003

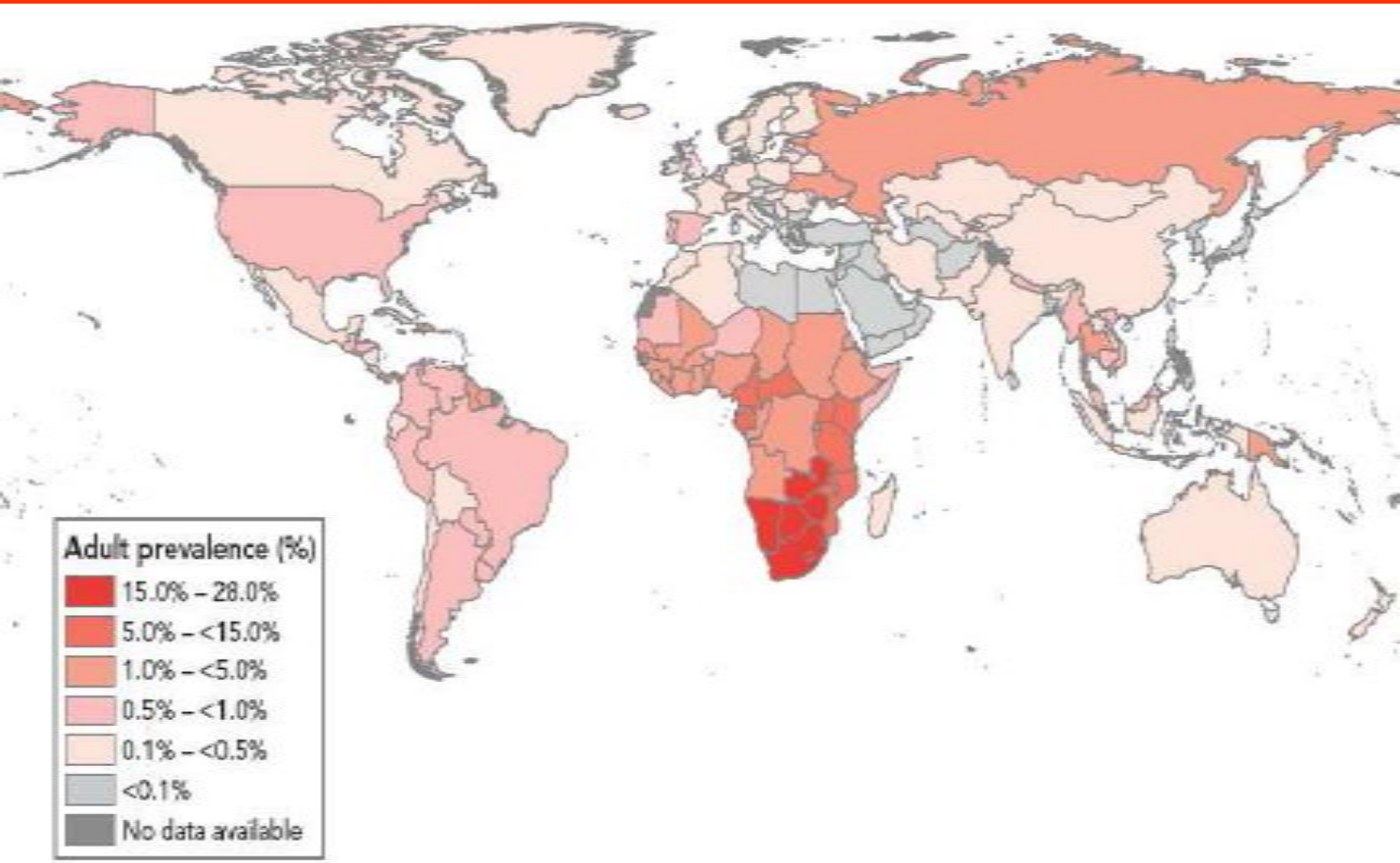
Total: 37.8 (34.6 – 42.3) million

UNAIDS

World Health Organization

00003-E-4 – July 2004

33MILLION (30-36) LIVING 2007



تقديرات الإصابة بالعدوى بفيروس الإيدز فى بلدان إقليم شرق المتوسط ٢٠٠٢ـ٢٠٠٢

البلد	العدد التقديرى للمعايشين للإيدز والعدوى بفيروسه خلال ٢٠٠٢ـ٢٠٠٢
أفغانستان	أقل من ١٠٠٠
البحرين	أقل من ١٠٠٠
قبرص	أقل من ١٠٠٠
جيبوتى	٨٢٨٣
مصر	٣٥٨٤
الجمهورية الإسلامية الإيرانية	٣٠,٠٠٠
العراق	أقل من ١٠٠٠
الأردن	أقل من ١٠٠٠
لبنان	١٩٥١
الكويت	أقل من ١٠٠٠
الجماهيرية العربية الليبية	٧٠٠٠
المغرب	١٤,٠٠٠
عمان	١٤٤٧
باكستان	٨٠,٠٠٠
فلسطين	أقل من ١٠٠٠
قطر	أقل من ١٠٠٠
المملكة العربية السعودية	٦٧٨٧ بينهم ١٥٠٩ سعودى الجنسية
الصومال	٤٣,٠٠٠
السودان	٥١٢,٠٠٠
الجمهورية العربية السورية	أقل من ١٠٠٠
تونس	أقل من ١٠٠٠
الإمارات المتحدة	أقل من ١٠٠٠
الجمهورية العربية اليمنية	١١,٢٢٧

نصف الدنيا
22/8/2004

Factors Enhance The Epidemics In Africa

A-Biological factors

B- Behavioral & social factors

A-Biological factors

- High rates of STDs with ulcers.
- Low rates of male circumcision.

How STDs Amplify HIV Transmission?

1-Ulceration.

2-Inflammation leads to increasing of:

- the conc. of HIV in genital secretions.
- the number of cells receptive to HIV.
- the number of receptors per cell.

The interaction between STDs & HIV is known as "Epidemiological Synergy".

B- Behavioral & social factors

- Little or no condom use.
- Multiple partners.
- Overlapping sexual partnership.
- Women’s economic dependence on marriage or prostitution, so unable to discus for safer sex.

HIV Life Cycle

A- Cell membrane:

Viral fusion & attachment:

-gp120 bind to CD4

-gp41 to CCR5 or CXCR4 (trigger fusion)

B- Intracytoplasmic:

- Entrance.
- Uncoating capsid .
- Reverse transcription of RNA to proviral DNA..

C- Intranuclear:

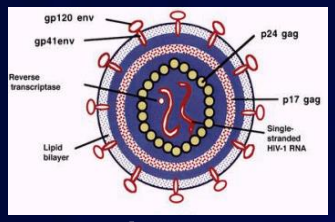
- Proviral DNA integrated with nucleus DNA. By (Integrase enzyme)
- Production of RNA genome & mRNA.

D-Outside the nucleus again

- Translation of mRNA to viral polyproteins.
- Cleavage of the polyproteins by protease enzyme into active viral polypeptide.
- Assembely between the viral genome & the viral polypeptide to form active proviron.

E-Cell membranes

Budding of the viron & coating by glycoprotein envelope.



Virus

CD4+

Cr 5

Uncoating

RNA

DNA

R.T.E

integrase

Viral genome

mRNA

Translation

Poly protein

mRNA

Budding

provirus

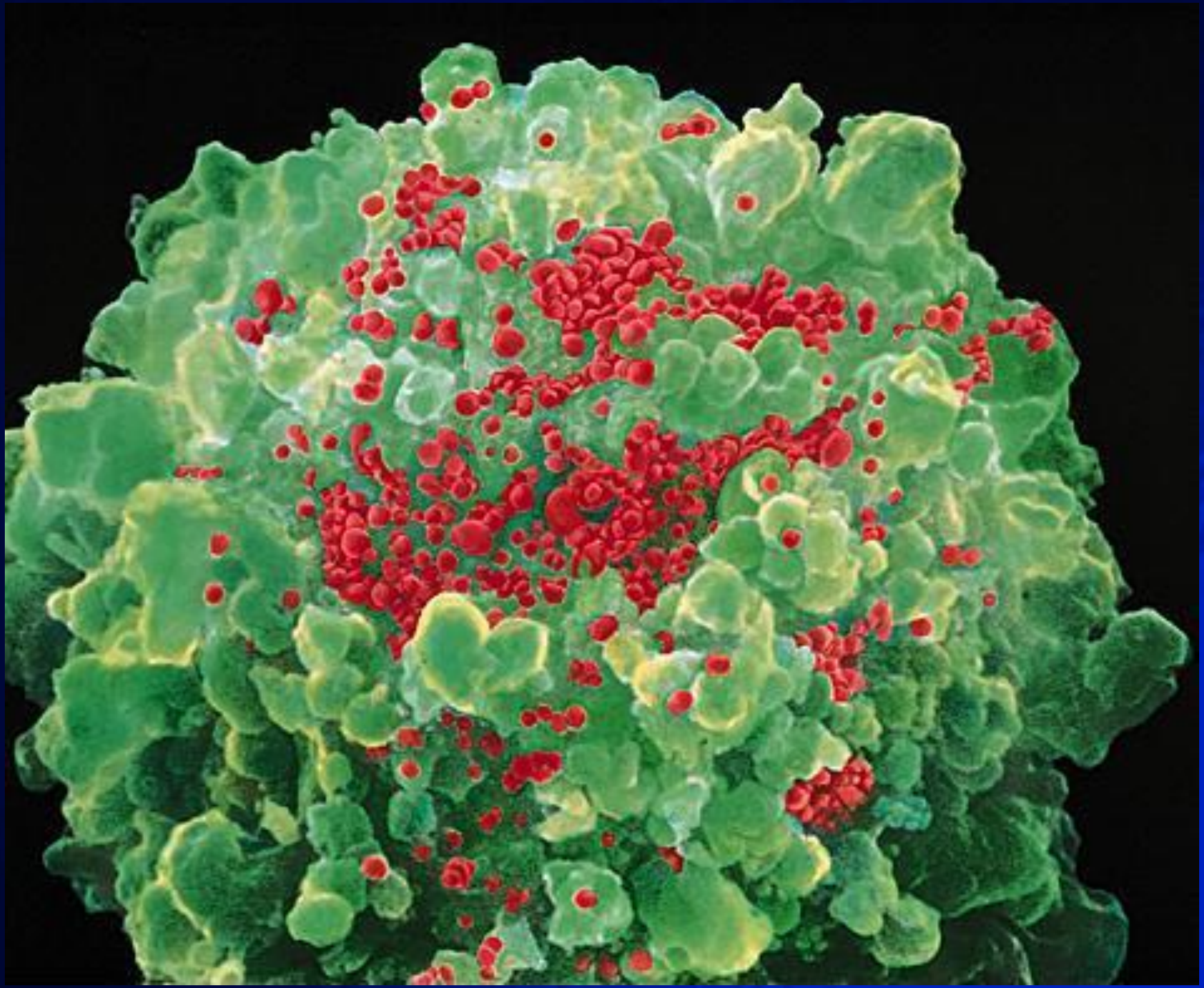
Viral genome

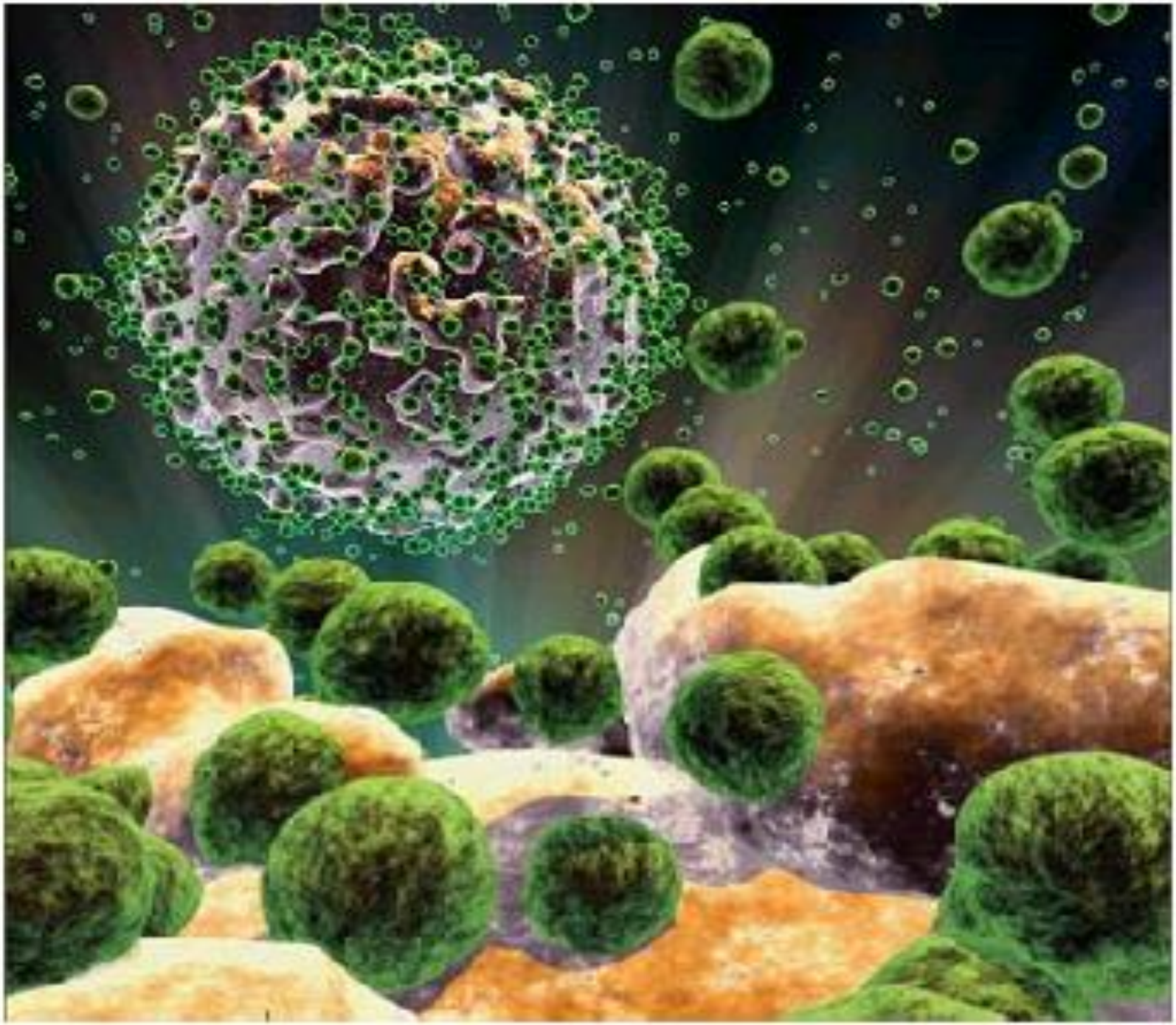
Protease enzym

Viral polypeptide

Assembly

Viruses





Immunology

- HIV binds to CD4 receptors on helper T-lymphocytes, monocytes, macrophages, and neural cells.
- The infected CD4+ migrates to the lymphoid tissue where the virus replicates producing billions of new virions.

- The released virions infect new CD4+ cells. As the infection progresses impaired function of CD4+ cells predisposes to the development of immune dysfunction.

The most common methods of transmission of HIV are:

Unprotected sex with an infected partner

Sharing needles with infected person

Almost eliminated as risk factors for HIV transmission are:

Transmission from infected mother to fetus

Infection from blood products

HIV Transmission: Global Summary

- Sexual intercourse: 70–80 %
  - (vaginal) (60–70) %
  - (anal) (5–10) %
- Injecting drug use 5–10 %
- Perinatal: 5–10 %
- Blood transfusion: 3–5%
- Health care (needlestick injury, etc.) <0.01%

Vertical transmission

- **Mothers with high viral load (durring acute influenza stage &/or aids) can infect their infants.**
- **Timing of infection:**
  - **Early phase of pregnancy is uncommon.**
  - **Late pregnancy is common.**
  - **During delivery by infected blood & genital secretions is very common while those delivered by C.S. have decreased incidence.**

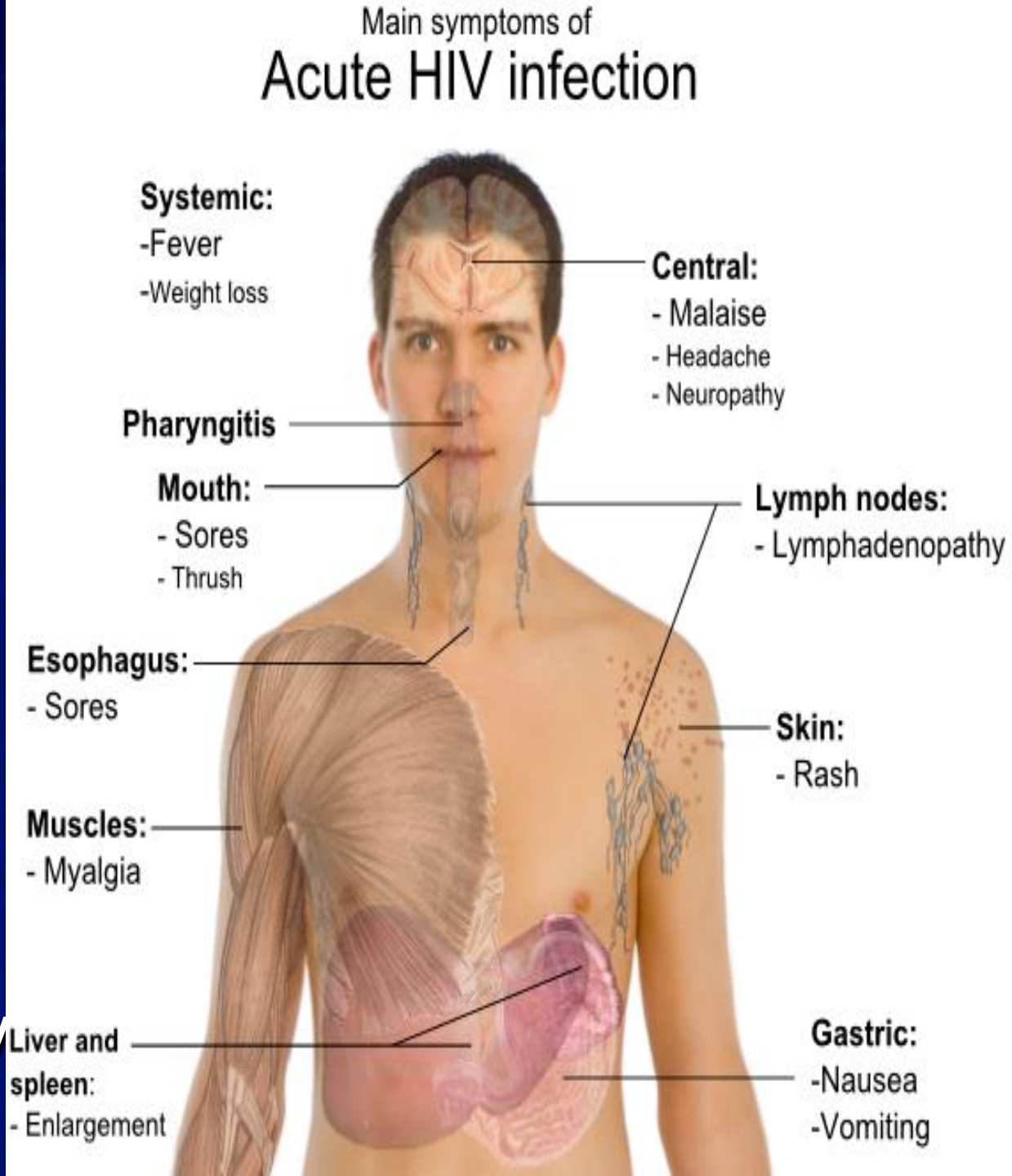
- Breast feeding:
  - Infants can be infected if the mother contract the HIV during breast-feeding or before pregnancy with high viral load.

N.B. Do not stop breast-feeding because infants will die from bottle-feeding.

Clinical Course

Acute HIV syndrome

- Influenza like.
- Develops 3-6 weeks after infection.
- Stays 1-2 weeks then resolve spontaneously



Cont.

- Vireamia (HVL) i.e. 10^9 virions are produced per day.
- Transient marked decline inCD4 cell count.
- Seroconversion i.e. positive Anti-HIV serology after spontaneous resolution of symptoms (6-8 weeks).

Asymptomatic Infection

- Positive serology.
- Low viral load due to intact immunity & trapping of the virus in lymph nodes.
- CD4 cell count may be variable.
- PGL.
- It lasts variable periods of time up to 10 years or more.

Q: When We Start ARVs Treatment in an Asymptomatic patients ?

A: When :

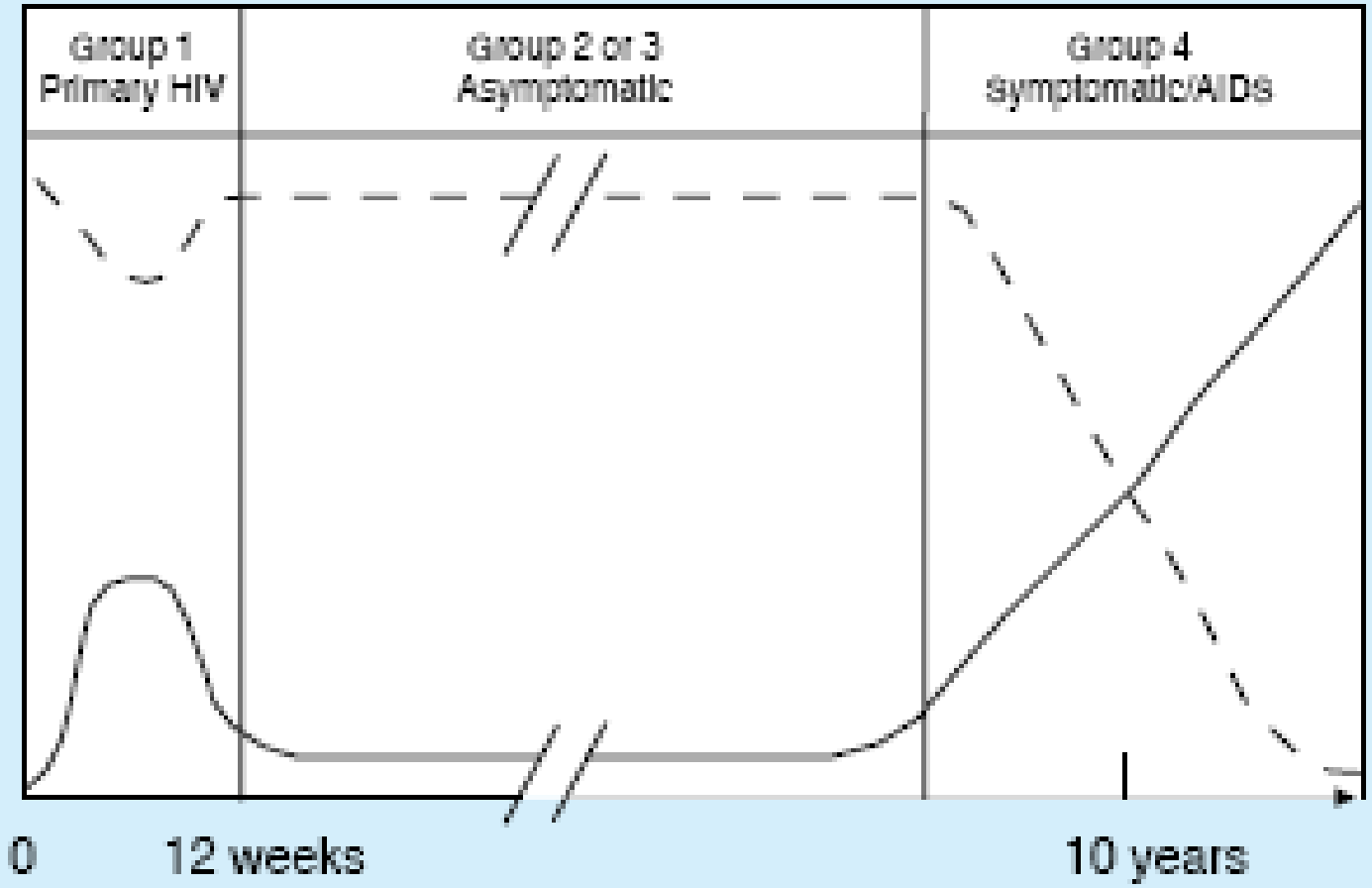
-CD4 T cell count 500 cells/ mm_3

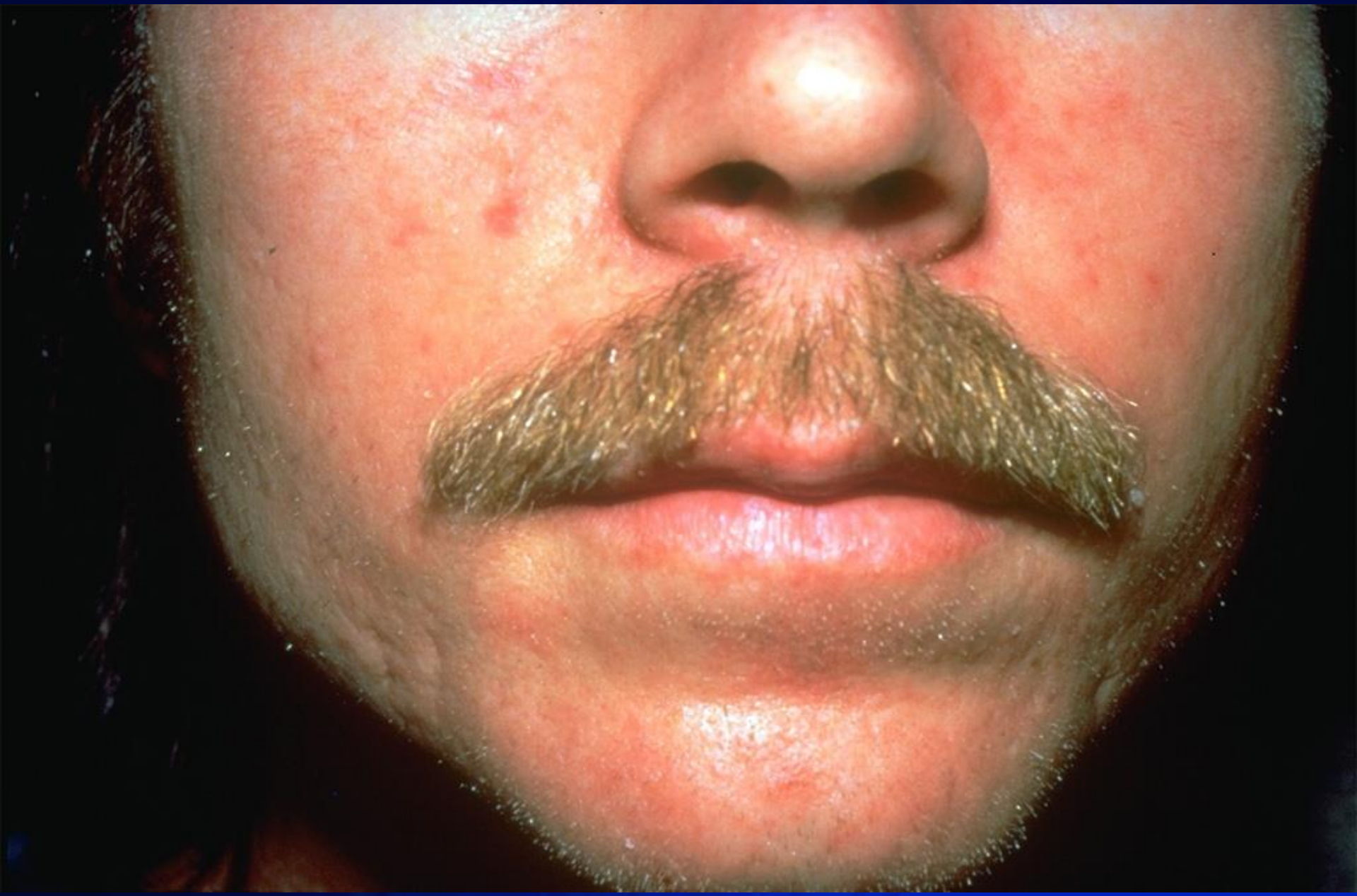
-The HIV-RNA level 10.000 copies /ml

(The International AIDS Society USA Panel Recommidation1997)

Symptomatic (AIDS)

- Early: oral candidiasis & hairy leucoplakia, prolonged fever, ch. Diarrhea, weight loss & seborrheic dermatitis.
- AIDs defining illness & opportunistic infections.
- CD4 cell count is less than 200/mm^3.
- HVL again due to lack of immunity.


Group 1
Primary HIV
Group 2 or 3
Asymptomatic
Group 4
Symptomatic/AIDS
0
12 weeks
10 years
Time after HIV infection
Viral load
CD4 lymphocyte levels



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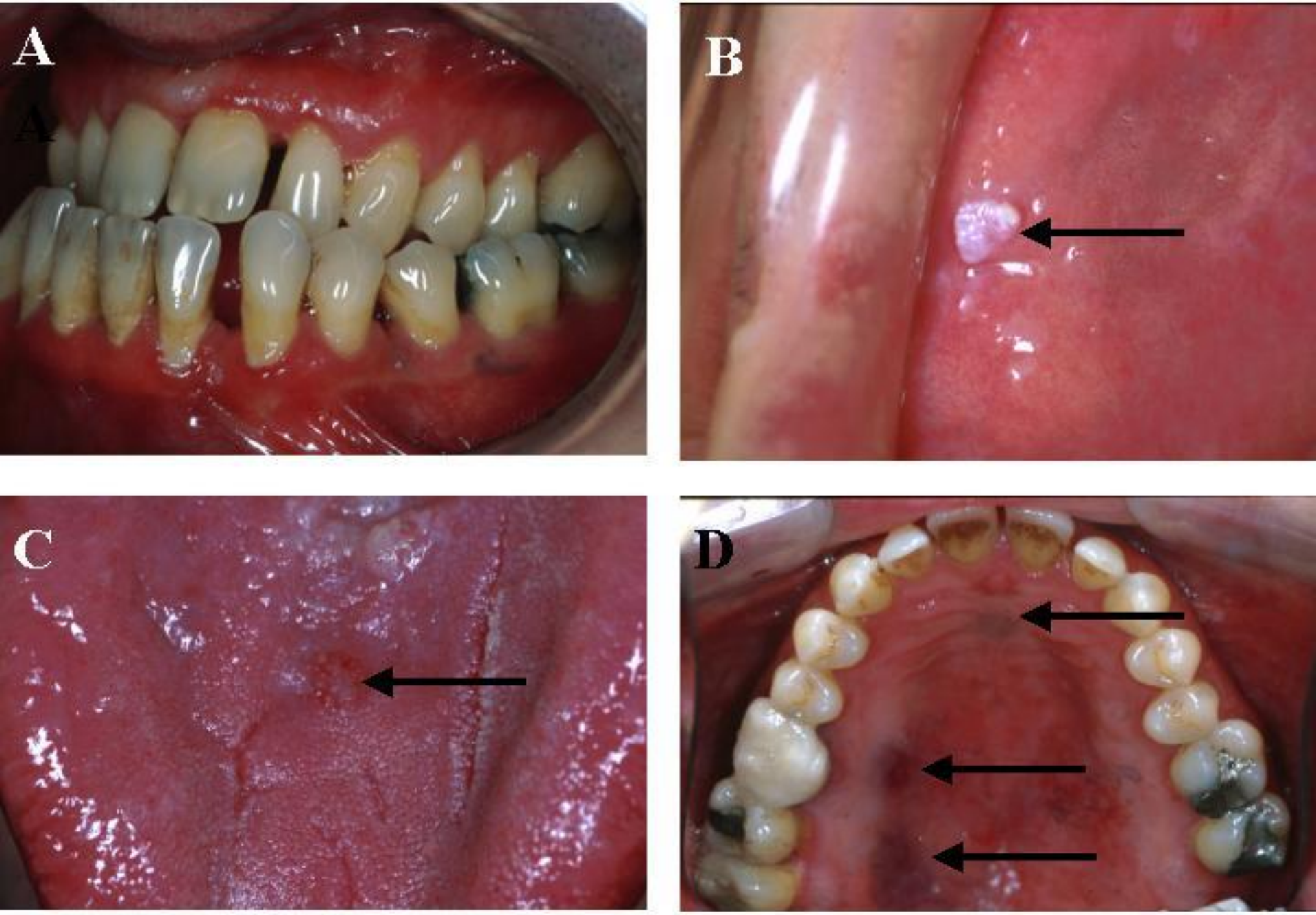

A
B
C
D

Case Definition for AIDS

All patients with:

- **CD4 less than 200cells / mm3**
- **AIDS indicator conditions e.g:**
  - **Pulmonary TB**
  - **Invasive cervical carcinoma**
  - **Recurrent pneumonia**
  - **Ch. Diarrhea & ch. Weight loss> 10%**
  - **Candidiasis of esophagus, trachea and bronchi.**

CDC(1993)

HIV Pathogenic Potential

1- Perinatally infected infants develop the disease in 6 months.

2- Transfusion patients of all age within 6 years.

3- Immunologically normal homosexual men in 10 years.

4- Transplant patients in 2 years.

5- Young patients with severs hemophilia in 14 years.

Factors Affecting Natural History of HIV Infection

A- Viral:

1- The dose of the infecting virus.

2- Viral cell tropism for specific cells.

3- Viral virulence according to the subtypes of it.

B- Non viral:

1- Immunologic state.

2- Psychosocial condition.

3- Alcoholism & drug abuse.

4- Previous or concurrent infections.

5- Associated STDs.

Laboratory Tests in HIV-infections

1- Diagnosis → By detection
- Antibodies
- Antigens

2. Monitoring of treatment or progression by
- CD4 count
- RNA test as PCR

1- Laboratory tests ; Diagnosis

A- *Detection of Antibodies:*

1-Screening test ELISA.

2-Confirmatory test (Western Blot) .

B- *Detection of Viral Antigen :*

1- Capture ELISA for 24 antigen.

2- PCR (non quantitative).

3- Immune complex –dissociated HIV.

4- Viral Culture .

HIV Diagnosis

A- Detection of HIV antibodies:

Seroconversion (detectable Abs) within 4 -12 weeks of acquiring the infection in > 95% of cases.

ELISA

- 1st step in diagnosis of HIV.
- The test have sensitivity of 99.9 %.
- But has false +ve in cases of : --
  -multiparous women &
  -polyclonal hypergammaglobinemia.

- **ELISA can detect HIV ABs in:**
  - **Serum:**
  - **Oral mucosotransudate (OMT)**
    - **An OMT sampling device, has been approved by FDA & its testing is equivalent to testing to serum.**

ELISA test

- Is available as a disposable kit for single test, so it can be used easily in clinics and small laboratories.

Confirmatory Tests

Western blot:

To detect defferent ABs to specific HIV proteins (GP41, P24, P55 or GP110 bands indicate a positive results for HIV infection).

B-Detection of Viral Antigen

1- Capture ELISA for P 24 antigen:

It is reliable to detect HIV infection one week before seroversion so reduce the window period.

2- PCR test (Non-quantitative):

-Diagnosis in rare cases when Abs &Ags P24 tests are negative.

-For mass screening.

-Test for blood donors to reduce window to 11 days but costly.

3-Immune complex -dissociated HIV:

(ICD- HIV)

To detect P 24 -core protein in **neonates** that may be masked by maternal Abs.

4- Viral culture:

It is possible, but not practical

Laboratory Tests in HIV-infections

1- Diagnosis → detection By

- Antibodies
- Antigens

2. Monitoring to treatment or progression by

- CD4 count
- RNR test as PCR

2- Monitoring tests to Monitor treatment or progression

1- CD4 T-cell count measurement

(Flow cytometry test)

2- RNA test quantitative.

Lab. Tests To Monitor Treatment or Progression

- ***CD4 T cell count test***

"Flow cytometry test"

It is a prognostic indicator in HIV patients,

It is used to:

A-determine when antiviral should be initiated.

B- determine when prophylaxis for Pneumocystic carnii starts.

C- monitor the efficacy of treatment.

2- HIV-RNA Quantitative test

Measuring viral load has become the marker of choice for therapeutic monitoring.

Methods:

1- Reverse transcriptase polymerase chain reaction (RT- PCR).
2- Neuclic acid-base sequence (NASBA).
3- Branched DNA (bDNA) assay.

N.B.

Viral RNA measurements are:

1-More direct.

2- More accurate.

3- More helpful markers than other markers:

- CD4 cell count.
- P24 antigen detection.

Why Antiviral Therapy?

- Reduce viral replication.
- Delay disease progression.
- Prolong survival.
- Intervention program:
  - to reduce the infectiousness.
  - postexposure prophylaxis.

FDA APROVED ANTIVIRALS IN 1990s

Category	Generic Name	Trade Name
Nucleoside reverse transcriptase **inhibitors** NRTIs	Zidovudine (ZDV, AZT)	Retrovir®
	Didanosine (ddI)	Videx®
	Zalcitabine (ddC)	Hivid®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir (ABC)	Ziagen®
	Zidovudine + Lamivudin	Combivir®
Non-nucleoside reverse transcriptase inhibitors NNRTIs	Nevirapine (NVP)	Viramune®
	Delavirdine (DLV)	Rescriptor®
	Efavirenz (EFV)	Sustiva®
Protease inhibitors (Pis)	Saquinavir (SQV)	Invirase®, Fortovase®
	Ritonavir (RTV)	Norvir®
	Indinavir (IDV)	Crixivan®
	Nelfinavir (NFV)	Viracept®
	Amprenavir (APV)	Agenerase®
Adjunctive medications	Hydroxyurea	Generic Hydrea®, Droxia®

The Viral key enzymes

1-RTC.
2- Integrase
.3-Protease

TTT are:
Inhibitors for these enzymes

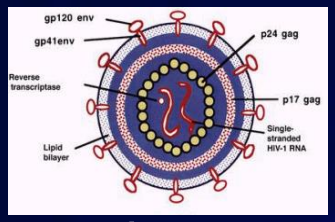
ANTI HIV therapy

- There are currently six classes of medications for treatment of HIV infection that block various stages of the HIV life cycle by targeting key enzymes.
- - **Reverse transcriptase inhibitors**

  (Nucleoside **NRTIs** & non N. **NNRTIs**.)
- - **Integrase inhibitors,& Protease inhibitors**

  prevent replication of the viral genome and intracellular viral maturation.
- **Fusion inhibitors and CCR5 antagonists**

  block the entry of virus into the CD4 cell either by interfering with viral fusion or co-receptor binding.



Virus

CD4

Cr-5

Uncoating

RNA

reverse transcriptase inhibitors

DNA

R.T.E

integrase

Translation

Poly protein

mRNA

Viral genome

mRNA

Budding

provirus

Protease inhibitors

Protease enzym

Viral genome

Viral polypeptide

Assembly

Viruses

Highly active antiretroviral therapy or HAART.

- Highly beneficial to many HIV-infected individuals
- Introduced, when the protease inhibitors initially became available in 1996
- Current HAART are combinations of at least three drugs belonging to at least two "classes," of antiretroviral agents

Initial Triple-drug Regimen

- 2 NRTIs and one PI.

OR

- 2NRTIs and 1 NNRTIs

Combination Therapy

- Monotherapy leads to drug resistance.
- Combination therapy examples:
  - 1st
    - Zidovudine 200mg t.d.s.
    - Didanosine 200mg b.i.d.
    - Nevirapine 200- 400mg once daily

Cont..

– 2nd

- Zidovudin 200mg t.d.s.
- Lamivudin 150 mg twice daily
- Indinavir 200mg t.d.s.

- The 1st is currently considered optimal with best efficacy, least side effects & lowest chance of selecting resistant mutant.

New classes of drugs : FDA approved 2007

1- Integrase inhibitors Raltegravir (Isentress®) **2- CCR5 antagonists (**Maraviroc (Selzentry®) treatment options for patients who are already resistant to common therapies,

they are:

- -expensive and
- -not widely avaibale.

THE EFFECT OF HAART

In countries where , the effective HAART is widely used ,There are :

- 1-Reduced the death rate HIV pts.
- 2-Increase their life expectancy ,

In addition to continuous spread of the disease these lead to increase of the number of HIV living persons .

Side Effects of ARVs

- **Headache, nausea, fatigue, peripheral neuritis, diarrhea and kidney stone.**
- **The cost of the triple-drug regimen is approximately $ 1.000/ month.**
- **But now, (2004 – UNAIDS) the regimen cost 300$/ year .**

Q: When The Patient Stops The ARVs Therapy?

A:

NO STOPPAGE.

Because stopping of the drug will lead to:

1- Virus breakthrough.

2- Drug resistant strains.

How HIV Can Be Turned into a Chronic Manageable Disease?

1. Combination therapy (HAART)& and early intervention.
2. Development of new highly active antiviral.
3. Viral load monitoring.
4. Opportunistic infections prophylaxis.

How to Reduce New Infections

A-Behavioral changes

- التمسك بالدين و الفضيلة

- Condom use.
- One partner only.
- Safer sex.

B-Biological intervention

- Vaccines.
- Topical microbicides
- Male circumcision.
- Use of antiviral therapy:
  - To reduce infectiousness.
  - Occupational exposure &needle-stick inj.
  - Postexposure prophylaxis

Vaccines

- **An ideal vaccine of HIV would work by increasing immunity of the susceptible host to prevent mucosal or systemic infection**
- **Conversely, if the vaccine is less than 100% effective, it could increase overall rates of transmission. (Why)**
- However, after over 20 years of research, HIV-1 remains a difficult target for a vaccine.

TOPICA MICROBICIDAL MUST BE:

1. Active against STDs pathogens & HIV.
2. Very limited toxicity.
3. Allow reproductive function.
4. Be acceptable for sexual intercourse.
5. Biologically difusable, adhesive & have long duration effect.
6. No systemic absorption.
7. No special storage.

NONOXYNOL-9 (N-9)

- It is the only topical microbicide in widespread use.
- It is a detergent can induce mucosal inflammation.
- NOW it is found that, (N-9) use increases the rate of HIV infection & has no protective effect against STDs. (WHY)

Circumcision

- In uncircumcised men ,the inner surface of the foreskin full of Langerhans' cells which have receptors to HIV.
- When men are circumcised; the mucosal tissue of the glans keratinizes & evolves into stratified squamous epithelium (resistant).

- Many countries in which all boys are circumcised before puberty have very limited epidemics.
- In countries with wider epidemics, circumcised men have lower HIV rates than uncircumcised men do.

ARVs Therapy to Reduce Infectiousness

- Starting combination therapy can reduce the viral load in the blood as well as in semen & genital secretions.

Occupational exposure and Needle-stick injury

Wash well; encourage bleeding;

do not suck or immerse in bleach.

LARGE inoculum (deep puncture from wide-bore needle causing bleeding).means

HIGH-RISK

Start ttt. within the first houre of puncture

and cont. for 4 weeks (zidovudin300mg&lamivudin 150mg twice daily and ininavir 800mg tds.)

ARVs Therapy as Postexposure Prophylaxis

- It is found that zidovudin reduced the acquisition of HIV in exposed healthcare workers.
- Postexposure prophylaxis has been offered to all victims of rape & subjects practice sex with infected partner. The antiviral should be taken within 72 hours of exposure.

- Routine use of drug therapy after sexual exposure has many objections:
  - Drug cost .
  - Toxicity .
  - Subjects are poorly adherent to postexposure prophylaxis.

GOLDEN RULES IN HIV THERAPY

- Aim to stop viral replication permanently.
- Monitor plasma viral load &CD_4 count, remembering that what seems like elimination often turns into reactivation when treatment stops.

Cont.

- Start ART.early before immunodeficiciency occurs
- Use of 3 antiviral drugs (minimizes replication & cross resistance.).
- Change to a new combination if plasma viral load rebounds.

THANK YOU